Manufacturing process information may be entitled to confidential treatment

Product ingredient source information may be entitled to confidential treatment

DP BARCODE: D357037; **FILE SYMBOL No.:** 35935-LG; **PRODUCT:** Fluroxypyr Technical

Date: February 24, 2009

SUBJECT: Product Chemistry Review of Fluroxypyr Technical TGAI / MUP

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DP BARCODE: D357037
DECISION No.: 400097
File Symbol No.: 35935-LG
PRODUCT: Fluroxypyr technical TGAI I / MUP
PCC: 128968
REGISTRANT: Nufarm Ltd.
USE: Herbicide
FOOD USE: Yes

INTRODUCTION:

The registrant Nufarm Ltd. has submitted a registration application for the new technical/mup product Fluroxypyr technical. The fluroxypyr technical TGAI / MUP is produced by [redacted]. In support of the application, the registrant has submitted 830 series group A and group B data with MRID Nos. 475407-01, 475407-03, and 475510-01, a CSF for basic formulation (dated 09-12-08) and the product label. TRB has been asked to evaluate the product chemistry data submitted and determine acceptability the data submitted.

SUMMARY OF FINDINGS:

1. The registrant has submitted a basic formulation CSF (dated 09-12-08) for fluroxypyr TGAI /MUP. The average purity of the active ingredient in TGAI/MUP is 97.0%, as determined by the five batch analysis. The proposed certified limits for the AI are based on the standard certified limits as set forth in 40CFR§158.350(b)(2). The proposed limits for impurities $\geq$ 0.1% are based on the preliminary analysis and expected to occur in normal commercial production. The product chemistry data submitted corresponding to guideline reference 830.1550 (product identity & composition) and 830.1750 (certified limits) satisfy the data requirements of 40CFR§158.320 and 158.350 respectively [MRID No. 475407-01].

2. The product chemistry data submitted corresponding to guideline reference 830.1600 (description of material used to produce the product) satisfy the data requirements of 40CFR§ 158.325 [MRID No. 475407-01].

3. The product chemistry data submitted corresponding to guideline reference 830.1620 (description of production process) satisfy the data requirements for 40CFR§158.330. The manufacturing process for fluroxypyr TGAI / mup consists of [redacted]. The applicant has provided the details of the chemical process with reaction conditions, equipment used, working up procedures, and quality assurance steps [MRID No. 475407-01].

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4. The product chemistry data submitted corresponding to guideline reference 830.1670 (discussion on the formation of impurities) satisfy the data requirements for 40CFR§158.340. During the production of fluroxypyr tgai/mup, the registrant discussed the formation of [redacted] major impurities present at the concentration of >0.1%. No other impurities were reported during the 5 batch analysis. The registrant has stated that there is no possibility of the formation of impurities of toxicological concern as there are no preexisting conditions or starting materials present in the production process which are required for their formation [MRID No. 475407-01].

5. The data submitted corresponding the guideline reference 830.1700 (preliminary analysis) satisfy the data requirements of 40CFR§158.345. The study was conducted under GLP requirements in compliance with 40CFR§160. The analysis study was performed by David Norris Laboratories, Ltd., Dartford, Kent, England on behalf of Nufarm UK Ltd. Five representative batches of the fluroxypyr tgai/mup [redacted] were analyzed for percent active ingredient and the [redacted] impurities were identified and quantified by using HPLC-UV with external standard quantification method. [redacted] of the [redacted] impurities were identified and quantified using HPLC with Conductivity detector with external standard method. [redacted]. The LOD's & LOQ's for all the impurities were determined. The analytical methods were validated for accuracy, linearity, and precision [MRID Nos. 475510-01].

6. The data submitted corresponding the guideline reference 830.1800 (enforcement analytical method) satisfy the data requirements of 40CFR§158.355. The purity of the AI in the TGAI was determined by HPLC-UV by external standard method. The analytical method utilized a Zorbax Eclipse, XDB-C8 column, 15 cm x 4.6 mm with UV detector operating at 225 nm. The method was validated for precision, accuracy and linearity [MRID Nos. 475407-01].

7. The data submitted corresponding to 830 series group B (physical-chemical properties) satisfy the data requirements of 40CFR§158.310 (e). The registrant has reported that studies for storage stability (830.6317) and corrosion characteristics (830.6320) are pending and will be submitted once completed (letter dated September 12, 2008) MRID No. 475407-03].

CONCLUSIONS:

The TRB has reviewed the product chemistry data submitted for fluroxypyr technical TGAI/MUP [redacted]) and has concluded that:

1. All the product chemistry data submitted & cited corresponding to the guidelines 830 Series group A and group B are acceptable, except for storage stability (830.6317), corrosion characteristics (830.6320), Oxidation/reduction (830.6314) and vapor pressure (830.7950).

2. The proposed CSF for basic formulation (dated 09-12-08) is acceptable.

3. The registrant must conduct the one year storage stability (830.6317) and corrosion characteristics (830.6320) for the proposed fluroxypyr technical tgai/mup under full GLP requirements. It is recommended that the observations should be made at the intervals of 0 (initial), 3 month, 6 month, 9 month, and 12 month (final). The results must be submitted to the Agency on completion.

4. The registrant must generate & submit the results of oxidation/reduction (830.6314) and vapor pressure studies (830.7950) for the fluroxypyr tgai/mup.

5. Few typo errors in naming of the impurities #2 & #6 (on page 26 of 69; MRID No. 475510-01) must be corrected. See Page #20 (confidential Appendix) of this report.

830.1550. Product identity & Composition: (MRID No. 475407-01)

Active Ingredient Identity:

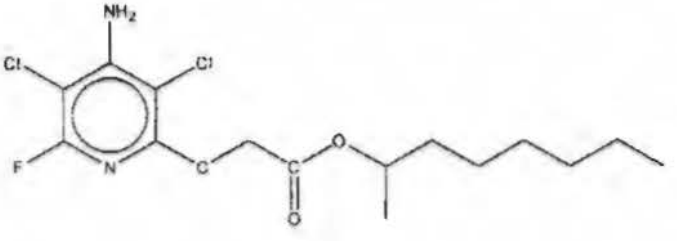
CAS No.:	81406-37-3
Common name/alias:	Fluroxypyr-meptyl
Chemical Names:	
IUPAC:	(*RS*)-1-methylheptyl 4-amino-3,5-dichloro-6-fluoro-2-pyridyloxyacetate
CAS:	1-methylheptyl [(4-amino-3,5-dichloro-6-fluoro-2-pyridinyl)oxy]acetate
Molecular formula:	$C_{15}H_{21}Cl_2FN_2O_3$
Molecular weight:	367.24
Structure:	

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Table 1. Manufacturing and Impurity Data for fluroxypyr technical TGAI / MUP

GLN	Requirement	MRID	Status	Details and /or Deficiency
830.1550	Product Identity and composition	Basic CSF (09-12-08)	A	The NC of AI (97.0%) is supported by 5 batch analysis & agrees with the label claim nominal concentration. [redacted]r impurities are listed on the CSF.
8301600	Description of materials used to produce the product	475407-01	A	The description & composition for all the starting materials used to produce the fluroxypyr technical [redacted] have been provided by the registrant
830.1620	Description of production process	475407-01	A	The AI was produced [redacted]. The production process has been described in full details.
830.1670	Discussion of formation of impurities	475407-01	A	The registrant has provided the complete mechanisms of formation, quantification and identification of all the impurities present at the levels of ≥ 0.1%.
830.1700	Preliminary analysis	475510-01	A	Five representative batches fluroxypyr technical ([redacted]) were analyzed for percent active ingredient and the impurities. The HPLC-UV in combination of HPLC-TC methods were used for the identification of the AI and the impurities. The five batch analysis supported the proposed CSF for basic formulation.
830.1750	Certified limits	475407-01	A	The proposed certified limits for the AI are based on standard certified limit table, whereas, those of impurities are based on five batch analysis.
830.1800	Enforcement analytical method	475407-01	A	The HPLC-UV (225 nm) with external standard method was used for the determination of the AI content in the TGAI/MUP. The method was validated for precision, linearity and accuracy..

A = Acceptable; N = unacceptable (see Deficiency); N/A = Not Applicable; G = Data gap; I = In progress or need upgrade; U = Up-grade (additional information required

830 Series group B (Physical-Chemical Properties)

Table 2: Physical and Chemical Properties of : Fluroxypyr technical TGAI / MUP (China)

GLN	Requirement	MRID	Status	Result or Deficiency
830.6302	Color	4754072-03	A	Off white
830.6303	Physical state	" " "	A	Solid
830.6304	Odor	" " "	A	Faint odor
830.6313	Stability to normal and elevated temperatures, metals, and metal ions	" " "	A	Stable (Fe and Al powder and the corresponding acetates at 54°C
830.6314	Oxidation/reduction: chemical incompatibility	" " "	G	Not submitted. Data is required
830.6315	Flammability		NA	
830.6316	Explodability		NA	
830.6317	Storage stability		G	1 year study required
830.6319	Miscibility		NA	
830.6320	Corrosion characteristics		G	1 year study required
830.7000	pH	475407-03	A	3.30
830.7050	UV/Visible absorption	" " "	A	**Note 1**
830.7100	Viscosity		NA	
830.7200	Melting point	475407-03	A	58.8°C
830.7220	Boiling point		NA	
830.7300	Density	475407-03	A	1.2451 g/ml @ 20°C
830.7370	Dissociation constants in water (DC)	" " "	A	No measurable DC could be determined
830.7550	Partition coefficient	" " "	A	Log Po/w = 5.41
830.7840	Water solubility:	" " "	A	Water = 0.155 mg/l
830.7950	Vapor pressure	" " "	G	Data is required

A = Acceptable; N = unacceptable (see Deficiency); N/A = Not Applicable; G = Data gap; I = In progress or need upgrade; U = Upgrade (additional information required); TBA = To Be Assigned

Note1. 830.7050 (UV/VIS): (MRID No. 475407-03)

Medium	Wavelength	ε value calculated
Neutral	210 nm	40673.4
Acidic	210 nm	41010.1
Alkaline	219 nm	23804.7

DP BARCODE: D357037; **FILE SYMBOL No.:** 35935-LG; **PRODUCT**: Fluroxypyr Technical

830.1800. Enforcement of analytical method: (MRID No. 474919-02)

Determination of AI by HPLC-UV method with external standard method

Determination of test substance purity, analytical procedure –

The five batches of NUP-06104 were assayed by a validated analytical method based on high performance liquid chromatography (HPLC) employing an external standard technique with ultraviolet (UV) detection.

The following conditions were used:

Instrument:	Jasco HPLC, pump 880PU, UV Detector 875-UV, Autosampler AS-950
Column:	XDB-C8 Zorbax Eclipse 15cm x 4.6 mm i.d.
Column temperature:	ambient
Mobile phase	70:30 Methanol: Purified water, isocratic
Flow rate:	1.0 mL/min
Injection volume:	10 µl
Detector:	UV set at 225 nm
Run Time:	60 min
Retention time observed for Fluroxypyr-meptyl:	Approximately 32 minutes

STANDARD PREPARATION

A primary reference standard of Fluroxypyr-meptyl was prepared at a concentration of 1.0 mg/mL in acetonitrile. This was subsequently used to prepare the working standards, which were prepared by dilution of the primary standard in acetonitrile. The concentrations of the respective working standards are shown below:

1. 1.0 mg/mL
2. 0.5 mg/mL
3. 0.2 mg/mL
4. 0.1 mg/mL
5. 0.05 mg/mL
6. 0.01 mg/mL

SAMPLE PREPARATION

All samples for this study were prepared from stock solutions stored in the refrigerator (4-8°C), and standards prepared fresh on the day of analysis.

ANALYSIS

The assay of Fluroxypyr-meptyl was performed using approximately 500 mg of each batch of technical material. The mass of the technical material was accurately recorded, transferred to a 100 ml volumetric flask (5 solutions in duplicate) and made up to volume with acetonitrile. These solutions were subsequently diluted by 1:10 and used for assay by injecting each duplicate solution once.

METHOD VALIDATION

The method was validated as reported in the preliminary analysis study, David Norris Analytical Laboratories Ltd., Laboratory Study # DNA0019.

Precision

The precision of this method was determined by making six replicate injections of a 0.5 mg/mL standard. A mean value of 0.503 mg/mL was found with an RSD of 0.697%.

Method Linearity

This method was demonstrated to be linear over the range from 0.01 – 1.0 mg/mL with a correlation coefficient of 0.9997.

A copy of this method with supporting chromatograms and results of the linearity and precision is in the preliminary analysis study for NUP-06104 as a part of this submission.

DP BARCODE: D357037; **FILE SYMBOL No.:** 35935-LG; **PRODUCT:** Fluroxypyr Technical

CONFIDENTIAL APPENDIX

Proposed basic CSF (dated 09-12-08)

[redacted]

8

Pages 9-20*Manufacturing process information may be entitled to confidential treatment*